



**IN THE UNITED STATES
PATENT AND TRADEMARK
OFFICE**

APPEAL BRIEF UNDER 37 C.F.R. § 1.192

In re the Application of: **GARVEY et al**
Application No.: **09/512,829**
Filed: **February 25, 2000**
Group Art Unit: **1624**
Examiner: **D. Rao**
For: **NITROSATED AND NITROSYLATED PROTON PUMP
INHIBITOR COMPOUNDS, COMPOSITIONS, AND
METHODS OF USE**
Attorney Docket No.: **102258.284**

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REAL PARTY IN INTEREST

Pursuant to an Assignment executed by each of the inventors and recorded in the U.S. Patent and Trademark Office at Reel 010624 Frame 0867, on February 24, 2000, and at Reel 010753 Frame 0210, on April 11, 2000, the Real Party in Interest is NitroMed, Inc.

II. RELATED APPEALS AND INTERFERENCES

The Appellants, the Appellants' legal representatives and the Assignee are not aware of any pending appeals or interferences that would directly or indirectly affect or have a bearing on the Board's decision in this appeal.

III. STATUS OF CLAIMS

During the course of prosecution, claims 1-35, 42-49, 52-58, 61-63, 65, 67, 69-78, 112 and 116 were canceled from the application without prejudice.

Claims 36-41, 50, 51, 59, 60, 64, 66, 68, 79-111, 113-115, 117 and 118 are currently pending in the application.

IV. STATUS OF AMENDMENTS

The U.S. Patent and Trademark Office (PTO) issued a final rejection dated July 2, 2003, to Appellants' amendment filed April 10, 2003. Appellants filed a Notice of Appeal from the final rejection on November 3, 2003.

Appellants filed concurrently herewith an Amendment under 37 CFR § 1.116 merely to correct the dependency of claims 90-92 and 95-98. In particular, "88" was changed to "89" in these amended claims. The claims presented in the Appendix assume that the Amendment under 37 CFR § 1.116 has been entered by the PTO.

V. SUMMARY OF INVENTION

The invention is based on the discovery of the effects of compounds that donate, transfer or release nitric oxide species *in vivo* together with one or more proton pump inhibitors. In particular, the invention is directed to the effects of compositions comprising at least one proton pump inhibitor or a pharmaceutically acceptable salt thereof, and (i) at least one S-nitrosothiol or (ii) at least one compound that donates, transfers or releases nitric oxide, induces endogenous production of nitric oxide or EDRF *in vivo*, stimulates endogenous synthesis of nitric oxide or is a substrate for nitric oxide synthesis (see specification at page 3, lines 24-29; page 50, lines 21-31; page 47, lines 4-16).

Improved gastroprotective properties, anti- *Helicobacter pylori* properties or antacid properties can be obtained by the use of the novel compounds and/or compositions of the invention (see specification at page 14, lines 24-30). Although proton pump inhibitors alone are effective in treating gastrointestinal disorders, they do not have any gastroprotective properties and, in addition, there is a high recurrence of ulcers associated with their use (see specification at page 16, lines 4-7).

Treatment or prevention of gastrointestinal disorders can also be obtained by the use of compounds and/or compositions of the invention. Such gastrointestinal disorders include, for example, Crohn's disease, ulcerative colitis, a peptic ulcer, a duodenal ulcer, infectious enteritis, colitis, diverticulitis, gastric hyperacidity, dyspepsia, gastroparesis, Zollinger-Ellison syndrome, gastroesophageal reflux disease, a *Helicobacter Pylori* associated disease, short-bowel syndrome, or a hypersecretory state associated with systemic mastocytosis or basophilic leukemia and hyperhistaminemia (see specification at page 15, lines 4-14; page 47, lines 4-16).

The methods of the invention also provide for decreasing or reversing gastrointestinal toxicity resulting from the administration of nonsteroidal antiinflammatory drugs (NSAIDs) and/or selective COX-2 inhibitors, facilitating ulcer healing resulting from the administration of NSAIDs and/or selective COX-2 inhibitors, and treating or preventing an ulcer by using the compounds and/or compositions of the invention (see specification at page 54, lines 7-22; page 47, lines 4-16). Optionally, the composition also comprises at least one nonsteroidal antiinflammatory drug and/or selective COX-2 inhibitor; wherein the nitric oxide donor and nonsteroidal antiinflammatory drug and/or selective COX-2 inhibitor are at least two different compounds (see specification at page 51, lines 25-30; page 52, lines 8-17).

Treatment of infections caused by *Helicobacter pylori* can also be obtained by administering to a patient at least one acid degradable antibacterial compound and the compounds and/or compositions of the invention (see specification at page 57, lines 29-32; page 58, lines 1-13, 23-32; page 59, lines 1-3).

Included in the invention are kits comprising the compounds and/or compositions of the invention (see specification at page 63, lines 29-32; page 64, lines 1-7).

VI. ISSUES

- A.** Are independent claims 50 and 64 and the claims dependent thereon (i.e., claims 36-41, 51 and 79-84) unobvious under 35 USC § 103 over Nohara et al (U.S. Patent No. 4,628,098) or Depui et al (WO 97/25064 or WO 96/24375) in view of Stamler et al (U.S. Patent No. 5,380,758)?
- B.** Are independent claims 66 and 85 and the claims dependent thereon (i.e., claims 36-41, 79-84, 86, 90-93 and 95-100) unobvious under 35 USC § 103 over Nohara et al (U.S. Patent No. 4,628,098) or Depui et al (WO 97/25064 or WO 96/24375) in view of Stamler et al (U.S. Patent No. 5,380,758)?
- C.** Is independent claim 68 and the claims dependent thereon (i.e., claims 36-41 and 79-84) unobvious under 35 USC § 103 over Nohara et al (U.S. Patent No. 4,628,098) or Depui et al (WO 97/25064 or WO 96/24375) in view of Stamler et al (U.S. Patent No. 5,380,758)?
- D.** Are independent claims 59, 87, 89 and 94 and the claims dependent thereon (i.e., 36-41, 60, 79-84, 88, 90-93 and 95-100) unobvious under 35 USC § 103 over Nohara et al (U.S. Patent No. 4,628,098) or Depui et al (WO 97/25064 or WO 96/24375) in view of Stamler et al (U.S. Patent No. 5,380,758)?
- E.** Are claims 101-111, 113-115, and 117-118 unobvious under 35 USC § 103 over Nohara et al (U.S. Patent No. 4,628,098) or Depui et al (WO 97/25064) in view of Stamler et al (U.S. Patent No. 5,380,758)?

VII. GROUPING OF CLAIMS

Independent claims 50 and 64 and the claims dependent thereon (i.e., claims 36-41, 51 and 79-84) stand or fall together.

Independent claims 66 and 85 and the claims dependent thereon (i.e., claims 36-41, 79-84, 86, 90-93 and 95-100) stand or fall together.

Independent claim 68 and the claims dependent thereon (i.e., claims 36-41 and 79-84) stand or fall together.

Independent claims 59, 87, 89, and 94 and the claims dependent thereon (i.e., 36-41, 60, 79-84, 88, 90-93 and 95-100) stand or fall together.

Claims 101-111, 113-115, and 117-118 stand or fall together.

VIII. ARGUMENTS

A. Introductory Remarks

The references cited by the PTO against Appellants' claims are the following:

(1) Nohara et al (US Patent No. 4,628,098) discloses benzimidazole compounds (e.g., proton pump inhibitors) for the prophylaxis and therapy of digestive ulcers (e.g. gastric ulcer, duodenal ulcer) and gastritis (Nohara at col. 6, lines 49-52).

(2) Depui '375 (WO 96/24375) discloses formulations comprising a proton pump inhibitor in combination with antibacterial compounds, and methods for the treatment of *Helicobacter pylori* infections (WO '375 at pages 1-3).

(3) Depui '064 (WO 97/25064) discloses formulations comprising a proton pump inhibitor in combination with a non-steroidal anti-inflammatory compound or an antacid formulation and methods for treating and preventing gastrointestinal disorders caused by a non-steroidal anti-inflammatory compound (WO '064 at pages 1-4). WO '064 discloses NO-releasing non-steroidal anti-inflammatory compounds that are in the form of a single chemical entity, i.e., a non-steroidal anti-inflammatory compound *covalently bonded to* an NO group (WO '064 at page 13, line 2).

(4) Stamler (US Patent No. 5,380,758) teaches the use of S-nitrosothiols for relaxing gastrointestinal smooth muscle for the treatment or prevention of achalasia, diarrhea, dumping syndrome and irritable bowel (Stamler at column 9, line 34 to column 10, line 62).

Based on these references, the PTO broadly asserts that the primary references (Nohara, Depui '375, Depui '064) are directed to methods of treating gastrointestinal disorders with proton pump inhibitors and the secondary reference (Stamler) is directed to methods of treating gastrointestinal disorders with S-nitrosothiols (i.e., NO donors) such that it would have been obvious to arrive at the present claims which are generally directed to methods of treating gastrointestinal disorders with proton pump inhibitors and NO donors.

In support of this conclusory rejection of the claims, the PTO refers to Appellants' "Provisional Response to Restriction Requirement and Request for Reconsideration of Restriction Requirement under 37 CFR § 1.143" filed March 25, 2003, where Appellants traversed the restriction requirement and stated "each of the specific methods of the independent claims are all related as they are directed to methods for the treatment and/or prevention of a

gastrointestinal disorder."¹ Appellants never made any admissions that the claims were obvious over each other or the prior art and never made any admissions that the independent claims, although generally directed to gastrointestinal disorders, were not different from each other in scope and/or content. Appellants were merely traversing a restriction requirement, and were not making any admissions as to the exact content of the claims in relation to each other or in relation to the prior art. The Appellants statements were not meant as a substitute to a substantive examination of the claims by the PTO. The PTO has refused to consider the actual teachings in the primary and secondary references and has refused to consider the actual language in the pending claims.

B. Independent claims 50 and 64 and the claims dependent thereon (i.e., claims 36-41, 51, and 79-84) are unobvious over Nohara, Depui '375 or Depui '064 in view of Stamler.

For the Board's convenience, independent claims 50 and 64 are reproduced below.

50. A method for improving the gastroprotective properties, the anti-*Helicobacter pylori* properties, or the antacid properties of a proton pump inhibitor comprising administering to a patient in need thereof a therapeutically effective amount of at least one proton pump inhibitor compound or a pharmaceutically acceptable salt thereof, and at least one compound that donates, transfers or releases nitric oxide, induces the production of endogenous nitric oxide or endothelium-derived relaxing factor, stimulates endogenous synthesis of nitric oxide or is a substrate for nitric oxide synthase.

64. A method for improving the gastroprotective properties, the anti-*Helicobacter* properties or the antacid properties of a proton pump inhibitor compound comprising administering to a patient in need thereof a therapeutically effective amount of at least one bismuth complex of at least one proton pump inhibitor compound and at least one compound that donates, transfers or releases nitric oxide, induces the production of endogenous nitric oxide or endothelium-derived relaxing factor, stimulates endogenous synthesis of nitric oxide or is a substrate for nitric oxide synthase.

The claims are unobvious over the cited references. Nohara, Depui '375 and Depui '064 are related to proton pump inhibitors; however, none of these references disclose or suggest methods for improving the gastroprotective properties, the anti-*Helicobacter* properties or the antacid properties of a proton pump inhibitor. Moreover, none of these references provide any motivation or suggestion to use compounds that donate, transfer or release nitric oxide, induce

¹ Final Office Action dated July 2, 2003, at page 5.

the production of endogenous nitric oxide or endothelium-derived relaxing factor, stimulate endogenous synthesis of nitric oxide or are a substrate for nitric oxide synthase (hereafter "NO donor") to improve the gastroprotective properties, the anti-*Helicobacter pylori* properties, or the antacid properties of a proton pump inhibitor.

Stamler does not cure the deficiencies in the primary references. Stamler teaches the use of S-nitrosothiols for relaxing gastrointestinal smooth muscle for the treatment or prevention of achalasia, diarrhea, dumping syndrome and irritable bowel (Stamler at column 9, line 34 to column 10, line 62). Stamler does not provide any motivation or suggestion to use S-nitrosothiols, or any other NO donor, to improve the gastroprotective properties, the anti-*Helicobacter* properties or the antacid properties of a proton pump inhibitor.

As the Federal Circuit held in *Velander v. Garner*, 68 USPQ2d 1769, 1772 (November 2003):

a proper analysis under § 103 requires, *inter alia*, consideration of two factors: (1) whether the prior art would have suggested to those of ordinary skill in the art that they should make the claimed composition or device, or carry out the claimed process; and (2) whether the prior art would also have revealed that in so making or carrying out, those of ordinary skill would have a reasonable expectation of success.

The Patent Office has not established either factor as required by the Federal Circuit. The record is devoid of any suggestion for one of ordinary skill to use an NO donor in combination with a proton pump inhibitor to improve the gastroprotective properties, the anti-*Helicobacter* properties or the antacid properties of the proton pump inhibitor.

Again, none of the primary references disclose NO donors, and Stamler does not disclose or suggest that S-nitrosothiols, or any other NO donor, would have the effect of improving the gastroprotective properties, the anti-*Helicobacter* properties or the antacid properties of a proton pump inhibitor. The Patent Office has not established a *prima facie* case of obviousness.²

Contrary to established case law and the MPEP, the PTO has not given the preamble of these claims any patentable weight. The preamble of the pending claims is essential to

² The Examiner points to Appellants' response filed March 25, 2003, wherein Appellants stated "each of the specific methods of the independent claims are all related as they are directed to methods for the treatment and/or prevention of a gastrointestinal disorder." Appellants respectfully submit this statement was given to traverse a restriction requirement issued by the Examiner and was not an admission regarding the patentability of the claimed methods in view of art generally teaching methods for the treatment and/or prevention of a gastrointestinal disorder and was not an admission regarding the relationship between the scope and/or content of the pending independent claims.

particularly point out the invention defined by the claims. *In re Bulloch*, 203 USPQ 171 (CCPA 1979); MPEP § 2111.02. Where the introductory phrase in a claim is used in a manner which adds an element of patentable significance to the claimed subject matter, as it does here, the preamble of a claim can render the claim patentable. *In re Benner*, 82 USPQ 49 (CCPA 1949); MPEP § 2111.02.

The limitations in a preamble are particularly relevant in method claims. In *Boehringer Ingelheim Vetmedica v. Schering-Plough Corp.*, 65 USPQ2d 1961, 1965 (Fed. Cir. 2003), the Federal Circuit held:

[A]s we explained in *Griffin v. Bertina*, 285 F.3d 1029, 62 USPQ2d 1431 (Fed. Cir. 2002), preamble language will limit the claim if it recites not merely a context in which the invention may be used, but the essence of the invention without which performance of the recited steps is nothing but an academic exercise. *Id.* at 1033, 62 USPQ2d at 1434. This principle holds true here, as it frequently does for method claims: "growing" and "isolating" are not merely circumstances in which the method may be useful, but instead are the *raison d'être* of the claimed method itself.

Contrary to the Federal Circuit's holding in *Boehringer Ingelheim Vetmedica*, the PTO has rendered the pending claims meaningless by improperly ignoring the preamble of the claims (i.e., improving the gastroprotective properties, the anti-*Helicobacter* properties or the antacid properties of a proton pump inhibitor). Without the preamble, there is not even a method recited in the pending claims.

The cited references do not disclose or suggest the presently claimed methods, and the PTO has not established a *prima facie* case of obviousness. In view thereof, Appellants request that the Board remand the application to the Examiner to enter a Notice of Allowance with respect to independent claims 50 and 64 and the claims dependent thereon (i.e., claims 36-41, 51, and 79-84).

C. Independent claims 66 and 85 and the claims dependent thereon (i.e., claims 36-41, 79-84, 86, 90-93 and 95-100 are unobvious over Nohara, Depui '375 or Depui '064 in view of Stamler.

For the Board's convenience, independent claims 66 and 85 are reproduced below.

66. A method for decreasing or reversing gastrointestinal toxicity or facilitating ulcer healing resulting from administration of a nonsteroidal antiinflammatory drug and/or a selective COX-2 inhibitor to a patient comprising administering to a patient in need thereof a therapeutically effective amount of at least one proton pump inhibitor compound, and at least

one compound that donates, transfers or releases nitric oxide, induces the production of endogenous nitric oxide or endothelium-derived relaxing factor, stimulates endogenous synthesis of nitric oxide or is a substrate for nitric oxide synthase, and, optionally, at least one nonsteroidal antiinflammatory drug and/or selective COX-2 inhibitor; wherein the at least one compound that donates, transfers or releases nitric oxide, induces the production of endogenous nitric oxide or endothelium-derived relaxing factor, stimulates endogenous synthesis of nitric oxide or is a substrate for nitric oxide synthase and the at least one nonsteroidal antiinflammatory drug and/or selective COX-2 inhibitor are at least two different compounds.

85. A method for decreasing or reversing gastrointestinal toxicity or facilitating ulcer healing resulting from administration of a nonsteroidal antiinflammatory drug and/or a selective COX-2 inhibitor in a patient in need thereof comprising administering a therapeutically effective amount of at least one proton pump inhibitor compound and at least one S-nitrosothiol.

The claims are unobvious over the cited references. Nohara and Depui '375 are related to proton pump inhibitors; however, Nohara and Depui '375 do not disclose or suggest methods for decreasing or reversing gastrointestinal toxicity or facilitating ulcer healing resulting from administration of a nonsteroidal antiinflammatory drug and/or a selective COX-2 inhibitor.

Depui '064 does not provide any motivation or suggestion to separately administer a proton pump inhibitor and an NO donor to decrease or reverse gastrointestinal toxicity or facilitate ulcer healing resulting from administration of a nonsteroidal antiinflammatory drug and/or a selective COX-2 inhibitor. Depui '064 does not disclose or suggest administering an NO donor that is a separate and distinct chemical entity from the nonsteroidal antiinflammatory drug.

Stamler does not cure the deficiencies of the primary references. Stamler teaches the use of S-nitrosothiols for relaxing gastrointestinal smooth muscle for the treatment or prevention of achalasia, diarrhea, dumping syndrome and irritable bowel (Stamler at column 9, line 34 to column 10, line 62). Stamler does not provide any motivation or suggestion to use S-nitrosothiols, or any other NO donor, to decrease or reverse gastrointestinal toxicity or to facilitate ulcer healing resulting from administration of a nonsteroidal antiinflammatory drug and/or a selective COX-2 inhibitor. The Patent Office has not established a *prima facie* case of obviousness.³

³ The Examiner points to Appellants' response filed March 25, 2003, wherein Appellants stated "each of the specific methods of the independent claims are all related as they are directed to methods for the treatment and/or prevention

As the Federal Circuit held in *Velander v. Garner*, 68 USPQ2d 1769, 1772 (November 2003):

a proper analysis under § 103 requires, *inter alia*, consideration of two factors: (1) whether the prior art would have suggested to those of ordinary skill in the art that they should make the claimed composition or device, or carry out the claimed process; and (2) whether the prior art would also have revealed that in so making or carrying out, those of ordinary skill would have a reasonable expectation of success.

The Patent Office has not established either factor as required by the Federal Circuit. The record is devoid of any suggestion to one of ordinary skill to use an NO donor in combination with a proton pump inhibitor to decrease or reverse gastrointestinal toxicity or to facilitate ulcer healing resulting from administration of a nonsteroidal antiinflammatory drug and/or a selective COX-2 inhibitor. Again, none of the primary references disclose NO donors, and Stamler does not disclose or suggest that S-nitrosothiols, or any other NO donor, would have the effect of decreasing or reversing gastrointestinal toxicity or facilitating ulcer healing resulting from administration of a nonsteroidal antiinflammatory drug and/or a selective COX-2 inhibitor. The Patent Office has not established a *prima facie* case of obviousness.⁴

Contrary to established case law and the MPEP, the PTO has not given the preamble of these claims any patentable weight. The preamble of the pending claims is essential to particularly point out the invention defined by the claims. *In re Bulloch*, 203 USPQ 171 (CCPA 1979); MPEP § 2111.02. Where the introductory phrase in a claim is used in a manner which adds an element of patentable significance to the claimed subject matter, as it does here, the preamble of a claim can render the claim patentable. *In re Benner*, 82 USPQ 49 (CCPA 1949); MPEP § 2111.02.

of a gastrointestinal disorder.” Appellants respectfully submit this statement was given to traverse a restriction requirement issued by the Examiner and was not an admission regarding the patentability of the claimed methods in view of related art generally teaching methods for the treatment and/or prevention of a gastrointestinal disorder and was not an admission regarding the relationship between the scope and/or content of the pending independent claims.

⁴ The Examiner points to Appellants’ response filed March 25, 2003, wherein Appellants stated “each of the specific methods of the independent claims are all related as they are directed to methods for the treatment and/or prevention of a gastrointestinal disorder.” Appellants respectfully submit this statement was given to traverse a restriction requirement issued by the Examiner and was not an admission regarding the patentability of the claimed methods in view of related art generally teaching methods for the treatment and/or prevention of a gastrointestinal disorder and was not an admission regarding the relationship between the scope and/or content of the pending independent claims.

The limitations in a preamble are particularly relevant in method claims. In *Boehringer Ingelheim Vetmedica v. Schering-Plough Corp.*, 65 USPQ2d 1961, 1965 (Fed. Cir. 2003), the Federal Circuit held:

[A]s we explained in *Griffin v. Bertina*, 285 F.3d 1029, 62 USPQ2d 1431 (Fed. Cir. 2002), preamble language will limit the claim if it recites not merely a context in which the invention may be used, but the essence of the invention without which performance of the recited steps is nothing but an academic exercise. *Id.* at 1033, 62 USPQ2d at 1434. This principle holds true here, as it frequently does for method claims: "growing" and "isolating" are not merely circumstances in which the method may be useful, but instead are the *raison d'être* of the claimed method itself.

Contrary to the Federal Circuit's holding in *Boehringer Ingelheim Vetmedica*, the PTO has rendered the pending claims meaningless by improperly ignoring the preamble of the claims (i.e., decreasing or reversing gastrointestinal toxicity or facilitating ulcer healing resulting from administration of a nonsteroidal antiinflammatory drug and/or a selective COX-2 inhibitor). Without the preamble, there is not even a method recited in the pending claims.

The cited references do not disclose or suggest the presently claimed methods, and the PTO has not established a *prima facie* case of obviousness. In view thereof, Appellants request that the Board remand the application to the Examiner to enter a Notice of Allowance with respect to independent claims 66 and 85 and the claims dependent thereon (i.e., claims 36-41, 79-84, 86, 90-93 and 95-100).

D. Independent claim 68 and the claims dependent thereon (i.e., claims 36-41 and 79-84) are unobvious over Nohara, Depui '375 or Depui '064 in view of Stamler.

Claim 68 is reproduced below for the Board's convenience.

68. A method for treating an infection caused by *Helicobacter pylori* comprising administering to a patient in need thereof a therapeutically effective amount of at least one acid degradable antibacterial compound, at least one proton pump inhibitor compound or a pharmaceutically acceptable salt thereof, and at least one compound that donates, transfers or releases nitric oxide, induces the production of endogenous nitric oxide or endothelium-derived relaxing factor, stimulates endogenous synthesis of nitric oxide or is a substrate for nitric oxide synthase.

The claims are unobvious over the cited references. Nohara and Depui '064 are related to proton pump inhibitors; however, neither reference disclose or suggests the use of proton pump inhibitors to treat *Helicobacter pylori* infections or to use an NO donor to treat *Helicobacter*

pylori infections. Accordingly, Nohara and Depui '064 are wholly unrelated to the claimed invention.

Depui '375 teaches the use of proton pump inhibitors in combination with antibacterial compounds to treat *Helicobacter pylori* infections. Depui '375 does not disclose or suggest the use of NO donors to treat *Helicobacter pylori* infections.

Stamler does not cure the deficiencies of the primary references. Stamler teaches the use of S-nitrosothiols for relaxing gastrointestinal smooth muscle for the treatment or prevention of achalasia, diarrhea, dumping syndrome and irritable bowel (Stamler at column 9, line 34 to column 10, line 62). Stamler does not provide any motivation or suggestion to use S-nitrosothiols or any other NO donors to treat an infection caused by *Helicobacter pylori*, and does not provide any motivation or suggestion to use S-nitrosothiols, or any other NO donor, in combination with a proton pump inhibitor to treat an infection caused by *Helicobacter pylori*.

As the Federal Circuit held in *Velander v. Garner*, 68 USPQ2d 1769, 1772 (November 2003):

a proper analysis under § 103 requires, *inter alia*, consideration of two factors: (1) whether the prior art would have suggested to those of ordinary skill in the art that they should make the claimed composition or device, or carry out the claimed process; and (2) whether the prior art would also have revealed that in so making or carrying out, those of ordinary skill would have a reasonable expectation of success.

The Patent Office has not established either factor as required by the Federal Circuit. The record is devoid of any suggestion to one of ordinary skill to use an NO donor in combination with a proton pump inhibitor to treat *Helicobacter pylori* infections. Again, none of the primary references disclose NO donors, and Stamler does not disclose or suggest that S-nitrosothiols, or any other NO donor, could be used to treat *Helicobacter pylori* infections. The Patent Office has not established a *prima facie* case of obviousness.⁵

Contrary to established case law and the MPEP, the PTO has not given the preamble of these claims any patentable weight. The preamble of the pending claims is essential to

⁵ The Examiner points to Appellants' response filed March 25, 2003, wherein Appellants stated "each of the specific methods of the independent claims are all related as they are directed to methods for the treatment and/or prevention of a gastrointestinal disorder." Appellants respectfully submit this statement was given to traverse a restriction requirement issued by the Examiner and was not an admission regarding the patentability of the claimed methods in view of related art generally teaching methods for the treatment and/or prevention of a gastrointestinal disorder and was not an admission regarding the relationship between the scope and/or content of the pending independent claims.

particularly point out the invention defined by the claims. *In re Bulloch*, 203 USPQ 171 (CCPA 1979); MPEP § 2111.02. Where the introductory phrase in a claim is used in a manner which adds an element of patentable significance to the claimed subject matter, as it does here, the preamble of a claim can render the claim patentable. *In re Benner*, 82 USPQ 49 (CCPA 1949); MPEP § 2111.02.

The limitations in a preamble are particularly relevant in method claims. In *Boehringer Ingelheim Vetmedica v. Schering-Plough Corp.*, 65 USPQ2d 1961, 1965 (Fed. Cir. 2003), the Federal Circuit held:

[A]s we explained in *Griffin v. Bertina*, 285 F.3d 1029, 62 USPQ2d 1431 (Fed. Cir. 2002), preamble language will limit the claim if it recites not merely a context in which the invention may be used, but the essence of the invention without which performance of the recited steps is nothing but an academic exercise. *Id.* at 1033, 62 USPQ2d at 1434. This principle holds true here, as it frequently does for method claims: "growing" and "isolating" are not merely circumstances in which the method may be useful, but instead are the *raison d'être* of the claimed method itself.

Contrary to the Federal Circuit's holding in *Boehringer Ingelheim Vetmedica*, the PTO has rendered the pending claims meaningless by improperly ignoring the preamble of the claims (i.e., treating an infection caused by *Helicobacter pylori*). Without the preamble, there is not even a method recited in the pending claims.

The cited references do not disclose or suggest the presently claimed methods, and the PTO has not established a *prima facie* case of obviousness. In view thereof, Appellants request that the Board remand the application to the Examiner to enter a Notice of Allowance with respect to independent claims 68 and the claims dependent thereon (i.e., claims 36-41 and 79-84).

E. Independent claims 59, 87, 89 and 94 and the claims dependent thereon (i.e., 36-41, 60, 79-84, 88, 90-93 and 95-100) are unobvious over Nohara, Depui '375 or Depui '064 in view of Stamler.

For the Board's convenience, independent claims 59, 87, 89 and 94 are reproduced below.

59. A method for preventing or treating a gastrointestinal disorder, wherein the gastrointestinal disorder is Crohn's disease, ulcerative colitis, a peptic ulcer, a stress ulcer, a bleeding peptic ulcer, a duodenal ulcer, infectious enteritis, colitis, diverticulitis, gastric hyperacidity, dyspepsia, gastroparesis, Zollinger-Ellison syndrome, gastroesophageal reflux disease, a *Helicobacter Pylori* associated disease, short-bowel syndrome, or a hypersecretory state associated with systemic mastocytosis or basophilic leukemia and

hyperhistaminemia; for facilitating ulcer healing, or for decreasing the recurrence of an ulcer in a patient in need thereof comprising administering to the patient a therapeutically effective amount of at least one proton pump inhibitor or a pharmaceutically acceptable salt thereof, and at least one compound that donates, transfers or releases nitric oxide, induces the production of endogenous nitric oxide or endothelium-derived relaxing factor, stimulates endogenous synthesis of nitric oxide or is a substrate for nitric oxide synthase.

87. A method for treating or preventing an ulcer in a patient in need thereof comprising administering a therapeutically effective amount of at least one proton pump inhibitor and at least one S-nitrosothiol.

89. A method for preventing or treating a gastrointestinal disorder, wherein the gastrointestinal disorder is Crohn's disease, ulcerative colitis, a peptic ulcer, a stress ulcer, a bleeding peptic ulcer, a duodenal ulcer, infectious enteritis, colitis, diverticulitis, gastric hyperacidity, dyspepsia, gastroparesis, Zollinger-Ellison syndrome, gastroesophageal reflux disease, a *Helicobacter Pylori* associated disease, short-bowel syndrome, or a hypersecretory state associated with systemic mastocytosis or basophilic leukemia and hyperhistaminemia; for facilitating ulcer healing, or for decreasing the recurrence of an ulcer in a patient in need thereof comprising administering to the patient a therapeutically effective amount of at least one proton pump inhibitor or a pharmaceutically acceptable salt thereof, and at least one S-nitrosothiol.

94. A method for treating or preventing a gastrointestinal disorder selected from the group consisting of Crohn's disease, ulcerative colitis, a stress ulcer, infectious enteritis, colitis, diverticulitis, gastric hyperacidity, gastroparesis, Zollinger-Ellison syndrome, gastroesophageal reflux disease, a *Helicobacter Pylori* associated disease, short-bowel syndrome, and a hypersecretory state associated with systemic mastocytosis or basophilic leukemia and hyperhistaminemia in a patient in need thereof comprising administering to the patient a therapeutically effective amount of at least one proton pump inhibitor or a pharmaceutically acceptable salt thereof, and at least one compound that donates, transfers or releases nitric oxide, induces the production of endogenous nitric oxide or endothelium-derived relaxing factor, stimulates endogenous synthesis of nitric oxide or is a substrate for nitric oxide synthase.

The claims are unobvious over the cited references. Nohara discloses the use of proton pump inhibitors for treating digestive ulcers (e.g., gastric ulcers, duodenal ulcers) and gastritis. Depui '064 discloses the use of proton pump inhibitors for treating side effects caused by

NSAIDs. Depui '375 discloses the use of proton pump inhibitors for the "treatment of disorders associated with *Helicobacter* infections" (page 1, line 6).

Stamler does not cure the deficiencies of the primary references. Stamler teaches the use of S-nitrosothiols for relaxing gastrointestinal smooth muscle for the treatment or prevention of achalasia, diarrhea, dumping syndrome and irritable bowel (Stamler at column 9, line 34 to column 10, line 62). Stamler does not provide any motivation or suggestion to use S-nitrosothiols, or any other NO donor, to treat or prevent ulcers, Crohn's disease, ulcerative colitis, a peptic ulcer, a stress ulcers, a bleeding peptic ulcer, a duodenal ulcer, infectious enteritis, colitis, diverticulitis, gastric hyperacidity, dyspepsia, gastroparesis, Zollinger-Ellison syndrome, gastroesophageal reflux disease, *Helicobacter Pylori* associated disease, short-bowel syndrome, or a hypersecretory state associated with systemic mastocytosis or basophilic leukemia and hyperhistaminemia; or to facilitate ulcer healing, or to decrease the recurrence of an ulcer.

The PTO makes the conclusory assertion that Stamler's methods of using S-nitrosothiols for relaxing gastrointestinal smooth muscle for the treatment or prevention of achalasia, diarrhea, dumping syndrome and irritable bowel would make it obvious to use S-nitrosothiols for the claimed methods of treating or preventing ulcers, Crohn's disease, ulcerative colitis, a peptic ulcer, a stress ulcers, a bleeding peptic ulcer, a duodenal ulcer, infectious enteritis, colitis, diverticulitis, gastric hyperacidity, dyspepsia, gastroparesis, Zollinger-Ellison syndrome, gastroesophageal reflux disease, *Helicobacter Pylori* associated disease, short-bowel syndrome, or a hypersecretory state associated with systemic mastocytosis or basophilic leukemia and hyperhistaminemia; or for facilitating ulcer healing, or decreasing the recurrence of an ulcer.

There is absolutely no overlap between the teachings in Stamler and the presently claimed methods of use. The PTO's assertions are nothing more than speculation. Mere speculation, without any evidentiary support, is not the proper basis for a rejection under § 103.

Again, as the Federal Circuit held in *Velandier v. Garner*, 68 USPQ2d 1769, 1772 (November 2003):

a proper analysis under § 103 requires, *inter alia*, consideration of two factors: (1) whether the prior art would have suggested to those of ordinary skill in the art that they should make the claimed composition or device, or carry out the claimed process; and (2) whether the prior art would also have revealed that in so making or carrying out, those of ordinary skill would have a reasonable expectation of success.

The Patent Office has not established either factor as required by the Federal Circuit. The record is devoid of any suggestion to one of ordinary skill to use an S-nitrosothiols in combination with a proton pump inhibitor to treat or prevent the claimed diseases. At page 4 in the final Office Action, the PTO asserts that (Emphasis in Original):

Stamler clearly teaches the use of the compounds in treating gastrointestinal disorders which include those of the esophagus, duodenum, sigmoid colon, etc. (see col. 9, lines 34-47). The instant claims also recite **gastroesophageal** reflux disease, colitis (i.e., inflammation of the mucous membrane of the **colon**), **duodenal** ulcer, etc. which involve the specific target areas discussed in Stamler and applicant has not provided any evidence to the contrary.

The PTO's argument is without merit. The burden is on the PTO to establish why one skilled in the art would arrive at the claimed invention based on the cited references. Contrary to the PTO's statements in the final office action, Stamler does not disclose or suggest gastroesophageal reflux disease, colitis or duodenal ulcers, and the PTO has provided absolutely no evidence why one skilled in the art would arrive at these specific diseases in view of the teachings in Stamler (column 9, lines 43-47) that:

S-nitrosothiols may be used for the treatment or prevention of gastrointestinal disorders. Disorders of the gastrointestinal tract include achalasia (spasm of the lower esophageal sphincter), diarrhea, dumping syndrome, and irritable bowel.

The PTO has made nothing more than overly broad, generalized and conclusory statements about the teachings in Stamler, that are completely unsupported by what Stamler actually teaches. Again, Stamler does not disclose or suggest treating or preventing any of the claimed diseases using S-nitrosothiols. The Patent Office has failed to establish a *prima facie* case of obviousness.⁶

The cited references do not disclose or suggest the presently claimed methods, and the PTO has not established a *prima facie* case of obviousness. In view thereof, Appellants request that the Board remand the application to the Examiner to enter a Notice of Allowance with

⁶ The Examiner points to Appellants' response filed March 25, 2003, wherein Appellants stated "each of the specific methods of the independent claims are all related as they are directed to methods for the treatment and/or prevention of a gastrointestinal disorder." Appellants respectfully submit this statement was given to traverse a restriction requirement and was not an admission regarding the patentability of the claimed methods in view of related art generally teaching methods for the treatment and/or prevention of a gastrointestinal disorder and was not an admission regarding the relationship between the scope and/or content of the pending independent claims.

respect to independent claims 59, 87, 89 and 94 and the claims dependent thereon (i.e., 36-41, 60, 79-84, 88, 90-93 and 95-100).

F. Claims 101-111, 113-115, and 117-118 are unobvious under 35 U.S.C. § 103 over Nohara or Depui '064 in view of Stamler.

Appellants respectfully submit that the cited references, alone and in combination, do not disclose or suggest the presently claimed invention. Nohara, Depui, and Stamler, discussed in detail above (the discussion of which is incorporated by reference herein in its entirety), do not disclose or suggest the presently claimed compositions and kits comprising at least one proton pump inhibitor or a pharmaceutically acceptable salt thereof and (i) at least one S-nitrosothiol or (ii) at least one compound that induces the production of endogenous nitric oxide or endothelium-derived relaxing factor, stimulates endogenous synthesis of nitric oxide or is a substrate for nitric oxide synthase.

Nohara and Depui teach the use of proton pump inhibitors but do not provide any motivation or suggestion to use proton pump inhibitors in combination with NO donors.

Stamler teaches the use of S-nitrosothiols for relaxing gastrointestinal smooth muscle but does not provide any motivation or suggestion to use S-nitrosothiols in combination with a proton pump inhibitor.

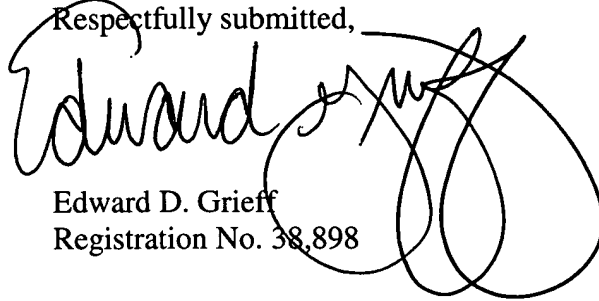
The Patent Office has not provided any evidence that any of the cited references provide any motivation to arrive at the compositions and kits of the claimed invention. Again, the reference must provide motivation for one to arrive at the claimed invention. *Gentry Gallery Inc. v. Berkline Corp.*, 45 USPQ2d 1498 (Fed. Cir. 1998); *In re Rouffet*, 47 USPQ2d 1453 (Fed. Cir. 1998).

In view of the above, Appellants request that the Board remand the application to the Examiner to enter a Notice of Allowance with respect to claims 101-111, 113-115, 117 and 118.

IX. CONCLUSION

Appellants request that the Board of Patent Appeals and Interferences reverse the outstanding rejections and remand the application to the Examiner to enter a Notice of Allowance for pending claims.

Respectfully submitted,

A large, stylized handwritten signature in black ink, appearing to read "Edward D. Grieff". The signature is written over the typed name and registration number.

Edward D. Grieff
Registration No. 38,898

Date: March 2, 2004

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X. APPENDIX**Pending Claims**

36. The method of claim 50, 59, 64, 66, 68, or 94, wherein the at least one proton pump inhibitor compound is a benzimidazole, a quinoline, a pyrimidine, a thiadiazole, a sulfinylnicotinamide, a thienoimidazole, or a imidazopyridine.

37. The method of claim 36, wherein the benzimidazole is omeprazole, lansoprazole, pantoprazole, rabeprazole, leminoprazole, timoprazole, tenatoprazole, disulprazole, esomeprazole, 2-(2-benzimidazolyl)-pyridine, a tricyclic imidazole, a thienopyridine benzimidazole, a fluoroalkoxy substituted benzimidazole, a dialkoxo benzimidazole, a N-substituted 2-(pyridylalkenesulfinyl) benzimidazole, a cycloheptenepyrindine, a 5-pyrrolyl-2-pyridylmethylsulfinyl benzimidazole, a alkylsulfinyl benzimidazole, a fluoro-pyridylmethylsulfinyl benzimidazole, an imidazo(4,5-b)pyridine, RO 18-5362 or IY 81149; wherein the quinoline is a 4-amino-3-carbonyl quinoline, a 4-amino-3-acylnaphthyride, a 4-aminoquinoline, a 4-amino-3-acylquinoline or a 3-butyryl-4-(2-methylphenylamino)-8-(2-hydroxyethoxy)quinoline; wherein the pyrimidine is a quinazoline, a tetrahydroisoquinolin-2-yl pyrimidine or YH 1885; wherein the thiadiazole is 3-substituted 1,2,4-thiadiazolo(4,5-a) benzimidazole or a 3-substituted imidazo(1,2-d)-thiadiazole; wherein the sulfinylnicotinamide is a 2-sulfinylnicotinamide; wherein the thienoimidazole is a pyridylsulfinylbenzimidazole, a pyridylsulfinyl thienoimidazole, a thienoimidazole-toluidine, a 4,5-dihydrooxazole, a thienoimidazole-toluidine or Hoe-731; wherein the imidazopyridine is a imidazo(1,2-a)pyridine, a pyrrolo(2,3-b)pyridine or a pharmaceutically acceptable salt thereof.

38. The method of claim 37, further comprising administering a pharmaceutically acceptable carrier.

39. The method of claim 50, 59, 64, 66, 68, or 94, wherein the compound that donates, transfers or releases nitric oxide, induces the production of endogenous nitric oxide or endothelium-derived relaxing factor, stimulates endogenous synthesis of nitric oxide or is a substrate for nitric oxide synthase is an S-nitrosothiol.

40. The method of claim 39, wherein the S-nitrosothiol is S-nitroso-N-acetylcysteine, S-nitroso-captopril, S-nitroso-N-acetylpenicillamine, S-nitroso-homocysteine, S-nitroso-cysteine or S-nitroso-glutathione.

41. The method of claim 39, wherein the S-nitrosothiol is:

- (i) $\text{HS}(\text{C}(\text{R}_e)(\text{R}_f))_m\text{SNO}$;
- (ii) $\text{ONS}(\text{C}(\text{R}_e)(\text{R}_f))_m\text{R}_e$; or
- (iii) $\text{H}_2\text{N}-\text{CH}(\text{CO}_2\text{H})-(\text{CH}_2)_m-\text{C}(\text{O})\text{NH}-\text{CH}(\text{CH}_2\text{SNO})-\text{C}(\text{O})\text{NH}-\text{CH}_2-\text{CO}_2\text{H}$;

wherein m is an integer from 2 to 20; R_e and R_f are each independently a hydrogen, an alkyl, a cycloalkoxy, a halogen, a hydroxy, an hydroxyalkyl, an alkoxyalkyl, an arylheterocyclic ring, an alkylaryl, a cycloalkylalkyl, a heterocyclicalkyl, an alkoxy, a haloalkoxy, an amino, an alkylamino, a dialkylamino, an arylamino, a diarylamino, an alkylarylamino, an alkoxyhaloalkyl, a haloalkoxy, a sulfonic acid, a sulfonic ester, an alkylsulfonic acid, an arylsulfonic acid, an arylalkoxy, an alkylthio, an arylthio, a cycloalkylthio, a cycloalkenyl, a cyano, an aminoalkyl, an aminoaryl, an aryl, an arylalkyl, an alkylaryl, a carboxamido, a alkylcarboxamido, an arylcarboxamido, an amidyl, a carboxyl, a carbamoyl, an alkylcarboxylic acid, an arylcarboxylic acid, an alkylcarbonyl, an arylcarbonyl, an ester, a carboxylic ester, an alkylcarboxylic ester, an arylcarboxylic ester, a haloalkoxy, a sulfonamido, an alkylsulfonamido, an arylsulfonamido, a sulfonic ester, a urea, a phosphoryl, a nitro, $-\text{T}-\text{Q}$, or $(\text{C}(\text{R}_e)(\text{R}_f))_k-\text{T}-\text{Q}$, or R_e and R_f taken together with the carbons to which they are attached form a carbonyl, a methanthial, a

heterocyclic ring, a cycloalkyl group or a bridged cycloalkyl group; Q is -NO or -NO₂; and T is independently a covalent bond, a carbonyl, an oxygen, -S(O)_o- or -N(R_a)R_i-, wherein o is an integer from 0 to 2, R_a is a lone pair of electrons, a hydrogen or an alkyl group; R_i is a hydrogen, an alkyl, an aryl, an alkylcarboxylic acid, an aryl carboxylic acid, an alkylcarboxylic ester, an arylcarboxylic ester, an alkylcarboxamido, an arylcarboxamido, an alkylaryl, an alkylsulfinyl, an alkylsulfonyl, an arylsulfinyl, an arylsulfonyl, a sulfonamido, a carboxamido, a carboxylic ester, an amino alkyl, an amino aryl, -CH₂-C(T-Q)(R_e)(R_f), or -(N₂O₂-)•M⁺, wherein M⁺ is an organic or inorganic cation; with the proviso that when R_i is -CH₂-C(T-Q)(R_e)(R_f) or -(N₂O₂-)•M⁺; then "-T-Q" can be a hydrogen, an alkyl group, an alkoxyalkyl group, an aminoalkyl group, a hydroxy group or an aryl group.

50. A method for improving the gastroprotective properties, the anti-*Helicobacter pylori* properties, or the antacid properties of a proton pump inhibitor comprising administering to a patient in need thereof a therapeutically effective amount of at least one proton pump inhibitor compound or a pharmaceutically acceptable salt thereof, and at least one compound that donates, transfers or releases nitric oxide, induces the production of endogenous nitric oxide or endothelium-derived relaxing factor, stimulates endogenous synthesis of nitric oxide or is a substrate for nitric oxide synthase.

51. The method of claim 50, further comprising administering to the patient a therapeutically effective amount of a bismuth-containing reagent.

59. A method for preventing or treating a gastrointestinal disorder, wherein the gastrointestinal disorder is Crohn's disease, ulcerative colitis, a peptic ulcer, a stress ulcer, a bleeding peptic ulcer, a duodenal ulcer, infectious enteritis, colitis, diverticulitis, gastric hyperacidity, dyspepsia, gastroparesis, Zollinger-Ellison syndrome, gastroesophageal reflux

disease, a *Helicobacter Pylori* associated disease, short-bowel syndrome, or a hypersecretory state associated with systemic mastocytosis or basophilic leukemia and hyperhistaminemia; for facilitating ulcer healing, or for decreasing the recurrence of an ulcer in a patient in need thereof comprising administering to the patient a therapeutically effective amount of at least one proton pump inhibitor or a pharmaceutically acceptable salt thereof, and at least one compound that donates, transfers or releases nitric oxide, induces the production of endogenous nitric oxide or endothelium-derived relaxing factor, stimulates endogenous synthesis of nitric oxide or is a substrate for nitric oxide synthase.

60. The method of claim 59, further comprising administering at least one antacid.

64. A method for improving the gastroprotective properties, the anti-*Helicobacter* properties or the antacid properties of a proton pump inhibitor compound comprising administering to a patient in need thereof a therapeutically effective amount of at least one bismuth complex of at least one proton pump inhibitor compound and at least one compound that donates, transfers or releases nitric oxide, induces the production of endogenous nitric oxide or endothelium-derived relaxing factor, stimulates endogenous synthesis of nitric oxide or is a substrate for nitric oxide synthase.

66. A method for decreasing or reversing gastrointestinal toxicity or facilitating ulcer healing resulting from administration of a nonsteroidal antiinflammatory drug and/or a selective COX-2 inhibitor to a patient comprising administering to a patient in need thereof a therapeutically effective amount of at least one proton pump inhibitor compound, and at least one compound that donates, transfers or releases nitric oxide, induces the production of endogenous nitric oxide or endothelium-derived relaxing factor, stimulates endogenous synthesis of nitric oxide or is a substrate for nitric oxide synthase, and, optionally, at least one nonsteroidal

antiinflammatory drug and/or selective COX-2 inhibitor; wherein the at least one compound that donates, transfers or releases nitric oxide, induces the production of endogenous nitric oxide or endothelium-derived relaxing factor, stimulates endogenous synthesis of nitric oxide or is a substrate for nitric oxide synthase and the at least one nonsteroidal antiinflammatory drug and/or selective COX-2 inhibitor are at least two different compounds.

68. A method for treating an infection caused by *Helicobacter pylori* comprising administering to a patient in need thereof a therapeutically effective amount of at least one acid degradable antibacterial compound, at least one proton pump inhibitor compound or a pharmaceutically acceptable salt thereof, and at least one compound that donates, transfers or releases nitric oxide, induces the production of endogenous nitric oxide or endothelium-derived relaxing factor, stimulates endogenous synthesis of nitric oxide or is a substrate for nitric oxide synthase.

79. The method of claim 50, 59, 64, 66, 68 or 94, wherein the at least one proton pump inhibitor compound or the pharmaceutically acceptable salt thereof, and the at least one compound that donates, transfers or releases nitric oxide, induces the production of endogenous nitric oxide or endothelium-derived relaxing factor, stimulates endogenous synthesis of nitric oxide or is a substrate for nitric oxide synthase are administered separately.

80. The method of claim 50, 59, 64, 66, 68, or 94, wherein the at least one proton pump inhibitor compound or the pharmaceutically acceptable salt thereof, and the at least one compound that donates, transfers or releases nitric oxide, induces the production of endogenous nitric oxide or endothelium-derived relaxing factor, stimulates endogenous synthesis of nitric oxide or is a substrate for nitric oxide synthase are administered together in the form of a composition.

81. The method of claim 50, 59, 64, 66, 68 or 94, wherein the at least one proton pump inhibitor compound or a pharmaceutically acceptable salt thereof, and the at least one compound that donates, transfers or releases nitric oxide, induces the production of endogenous nitric oxide or endothelium-derived relaxing factor, stimulates endogenous synthesis of nitric oxide or is a substrate for nitric oxide synthase are administered orally, buccally, topically, by injection, by inhalation, or by transdermal application.

82. The method of claim 81, wherein the at least one proton pump inhibitor compound or a pharmaceutically acceptable salt thereof, and the at least one compound that donates, transfers or releases nitric oxide, induces the production of endogenous nitric oxide or endothelium-derived relaxing factor, stimulates endogenous synthesis of nitric oxide or is a substrate for nitric oxide synthase are administered orally in a solid dosage form or a liquid dosage form.

83. The method of claim 82, wherein the solid dosage form is a capsule, a tablet, an effervescent tablet, a chewable tablet, a pill, a powder, a sachet, a granule or a gel.

84. The method of claim 82, wherein the liquid dosage form is an emulsion, a solution, a suspension, a syrup, or an elixir.

85. A method for decreasing or reversing gastrointestinal toxicity or facilitating ulcer healing resulting from administration of a nonsteroidal antiinflammatory drug and/or a selective COX-2 inhibitor in a patient in need thereof comprising administering a therapeutically effective amount of at least one proton pump inhibitor compound and at least one S-nitrosothiol.

86. The method of claim 85, further comprising administering a therapeutically effective amount of at least one nonsteroidal antiinflammatory drug and/or selective COX-2 inhibitor.

87. A method for treating or preventing an ulcer in a patient in need thereof comprising administering a therapeutically effective amount of at least one proton pump inhibitor and at least one S-nitrosothiol.

88. The method of claim 87, wherein the ulcer is a peptic ulcer, a stress ulcer, a bleeding peptic ulcer, a duodenal ulcer, or gastritis.

89. A method for preventing or treating a gastrointestinal disorder, wherein the gastrointestinal disorder is Crohn's disease, ulcerative colitis, a peptic ulcer, a stress ulcer, a bleeding peptic ulcer, a duodenal ulcer, infectious enteritis, colitis, diverticulitis, gastric hyperacidity, dyspepsia, gastroparesis, Zollinger-Ellison syndrome, gastroesophageal reflux disease, a *Helicobacter Pylori* associated disease, short-bowel syndrome, or a hypersecretory state associated with systemic mastocytosis or basophilic leukemia and hyperhistaminemia; for facilitating ulcer healing, or for decreasing the recurrence of an ulcer in a patient in need thereof comprising administering to the patient a therapeutically effective amount of at least one proton pump inhibitor or a pharmaceutically acceptable salt thereof, and at least one S-nitrosothiol.

90. The method of claim 85, 87 or 89, wherein the S-nitrosothiol is S-nitroso-N-acetylcysteine, S-nitroso-captopril, S-nitroso-N-acetylpenicillamine, S-nitroso-homocysteine, S-nitroso-cysteine or S-nitroso-glutathione.

91. The method of claim 85, 87 or 89, wherein the S-nitrosothiol is:

(i) $\text{HS}(\text{C}(\text{R}_e)(\text{R}_f))_m\text{SNO}$;

(ii) $\text{ONS}(\text{C}(\text{R}_e)(\text{R}_f))_m\text{R}_e$; or

(iii) $\text{H}_2\text{N}-\text{CH}(\text{CO}_2\text{H})-(\text{CH}_2)_m-\text{C}(\text{O})\text{NH}-\text{CH}(\text{CH}_2\text{SNO})-\text{C}(\text{O})\text{NH}-\text{CH}_2-\text{CO}_2\text{H}$;

wherein m is an integer from 2 to 20; R_e and R_f are each independently a hydrogen, an alkyl, a cycloalkoxy, a halogen, a hydroxy, an hydroxyalkyl, an alkoxyalkyl, an arylheterocyclic ring, an

alkylaryl, a cycloalkylalkyl, a heterocyclicalkyl, an alkoxy, a haloalkoxy, an amino, an alkylamino, a dialkylamino, an arylamino, a diarylamino, an alkylarylamino, an alkoxyhaloalkyl, a haloalkoxy, a sulfonic acid, a sulfonic ester, an alkylsulfonic acid, an arylsulfonic acid, an arylalkoxy, an alkylthio, an arylthio, a cycloalkylthio, a cycloalkenyl, a cyano, an aminoalkyl, an aminoaryl, an aryl, an arylalkyl, an alkylaryl, a carboxamido, a alkylcarboxamido, an arylcarboxamido, an amidyl, a carboxyl, a carbamoyl, an alkylcarboxylic acid, an arylcarboxylic acid, an alkylcarbonyl, an arylcarbonyl, an ester, a carboxylic ester, an alkylcarboxylic ester, an arylcarboxylic ester, a haloalkoxy, a sulfonamido, an alkylsulfonamido, an arylsulfonamido, a sulfonic ester, a urea, a phosphoryl, a nitro, -T-Q, or $(C(R_e)(R_f))_k$ -T-Q, or R_e and R_f taken together with the carbons to which they are attached form a carbonyl, a methanthial, a heterocyclic ring, a cycloalkyl group or a bridged cycloalkyl group; Q is -NO or -NO₂; and T is independently a covalent bond, a carbonyl, an oxygen, -S(O)_o- or -N(R_a)R_i-, wherein o is an integer from 0 to 2, R_a is a lone pair of electrons, a hydrogen or an alkyl group; R_i is a hydrogen, an alkyl, an aryl, an alkylcarboxylic acid, an aryl carboxylic acid, an alkylcarboxylic ester, an arylcarboxylic ester, an alkylcarboxamido, an arylcarboxamido, an alkylaryl, an alkylsulfinyl, an alkylsulfonyl, an arylsulfinyl, an arylsulfonyl, a sulfonamido, a carboxamido, a carboxylic ester, an amino alkyl, an amino aryl, -CH₂-C(T-Q)(R_e)(R_f), or -(N₂O₂)⁻•M⁺, wherein M⁺ is an organic or inorganic cation; with the proviso that when R_i is -CH₂-C(T-Q)(R_e)(R_f) or -(N₂O₂)⁻•M⁺; then "-T-Q" can be a hydrogen, an alkyl group, an alkoxyalkyl group, an aminoalkyl group, a hydroxy group or an aryl group.

92. The method of claim 85, 87 or 89, wherein the at least one proton pump inhibitor compound is a benzimidazole, a quinoline, a pyrimidine, a thiadiazole, a sulfinylnicotinamide, a thienoimidazole, or a imidazopyridine.

93. The method of claim 91, wherein the benzimidazole is omeprazole, lansoprazole, pantoprazole, rabeprazole, leminoprazole, timoprazole, tenatoprazole, disulprazole, esomeprazole, 2-(2-benzimidazolyl)-pyridine, a tricyclic imidazole, a thienopyridine benzimidazole, a fluoroalkoxy substituted benzimidazole, a dialkoxo benzimidazole, a N-substituted 2-(pyridylalkenesulfinyl) benzimidazole, a cycloheptenepyrindine, a 5-pyrrolyl-2-pyridylmethylsulfinyl benzimidazole, a alkylsulfinyl benzimidazole, a fluoro-pyridylmethylsulfinyl benzimidazole, an imidazo(4,5-b)pyridine, RO 18-5362 or IY 81149; wherein the quinoline is a 4-amino-3-carbonyl quinoline, a 4-amino-3-acylnaphthyride, a 4-aminoquinoline, a 4-amino-3-acylquinoline or a 3-butyryl-4-(2-methylphenylamino)-8-(2-hydroxyethoxy)quinoline; wherein the pyrimidine is a quinazoline, a tetrahydroisoquinolin-2-yl pyrimidine or YH 1885; wherein the thiadiazole is 3-substituted 1,2,4-thiadiazolo(4,5-a) benzimidazole or a 3-substituted imidazo(1,2-d)-thiadiazole; wherein the sulfinylnicotinamide is a 2-sulfinylnicotinamide; wherein the thienoimidazole is a pyridylsulfinylbenzimidazole, a pyridylsulfinyl thienoimidazole, a theinoimidazole-toluidine, a 4,5-dihydrooxazole, a thienoimidazole-toluidine or Hoe-731; wherein the imidazopyridine is a imidazo(1,2-a)pyridine, a pyrrolo(2,3-b)pyridine or a pharmaceutically acceptable salt thereof.

94. A method for treating or preventing a gastrointestinal disorder selected from the group consisting of Crohn's disease, ulcerative colitis, a stress ulcer, infectious enteritis, colitis, diverticulitis, gastric hyperacidity, gastroparesis, Zollinger-Ellison syndrome, gastroesophageal reflux disease, a *Helicobacter Pylori* associated disease, short-bowel syndrome, and a hypersecretory state associated with systemic mastocytosis or basophilic leukemia and hyperhistaminemia in a patient in need thereof comprising administering to the patient a therapeutically effective amount of at least one proton pump inhibitor or a pharmaceutically

acceptable salt thereof, and at least one compound that donates, transfers or releases nitric oxide, induces the production of endogenous nitric oxide or endothelium-derived relaxing factor, stimulates endogenous synthesis of nitric oxide or is a substrate for nitric oxide synthase.

95. The method of claim 85, 87 or 89, wherein the at least one proton pump inhibitor compound or the pharmaceutically acceptable salt thereof, and the at least one S-nitrosothiol are administered separately.

96. The method of claim 85, 87 or 89, wherein the at least one proton pump inhibitor compound or the pharmaceutically acceptable salt thereof, and the at least one S-nitrosothiol are administered together in the form of a composition.

97. The method of claim 85, 87 or 89, wherein the at least one proton pump inhibitor compound or a pharmaceutically acceptable salt thereof, and the at least one S-nitrosothiol are administered orally, buccally, topically, by injection, by inhalation, or by transdermal application.

98. The method of claim 85, 87 or 89, wherein the at least one proton pump inhibitor compound or a pharmaceutically acceptable salt thereof, and the at least S-nitrosothiol are administered orally in a solid dosage form or a liquid dosage form.

99. The method of claim 98, wherein the solid dosage form is a capsule, a tablet, an effervescent tablet, a chewable tablet, a pill, a powder, a sachet, a granule or a gel.

100. The method of claim 98, wherein the liquid dosage form is an emulsion, a solution, a suspension, a syrup, or an elixir.

101. A composition comprising at least one proton pump inhibitor or a pharmaceutically acceptable salt thereof and at least one S-nitrosothiol.

102. The composition of claim 101, wherein the S-nitrosothiol is S-nitroso-N-acetylcysteine, S-nitroso-captopril, S-nitroso-N-acetylpenicillamine, S-nitroso-homocysteine, S-nitroso-cysteine or S-nitroso-glutathione.

103. The composition of claim 101, wherein the S-nitrosothiol is:

- (i) $\text{HS}(\text{C}(\text{R}_e)(\text{R}_f))_m\text{SNO}$;
- (ii) $\text{ONS}(\text{C}(\text{R}_e)(\text{R}_f))_m\text{R}_e$; or
- (iii) $\text{H}_2\text{N}-\text{CH}(\text{CO}_2\text{H})-(\text{CH}_2)_m-\text{C}(\text{O})\text{NH}-\text{CH}(\text{CH}_2\text{SNO})-\text{C}(\text{O})\text{NH}-\text{CH}_2-\text{CO}_2\text{H}$;

wherein m is an integer from 2 to 20; R_e and R_f are each independently a hydrogen, an alkyl, a cycloalkoxy, a halogen, a hydroxy, an hydroxyalkyl, an alkoxyalkyl, an arylheterocyclic ring, an alkylaryl, a cycloalkylalkyl, a heterocyclicalkyl, an alkoxy, a haloalkoxy, an amino, an alkylamino, a dialkylamino, an arylamino, a diarylamino, an alkylarylamino, an alkoxyhaloalkyl, a haloalkoxy, a sulfonic acid, a sulfonic ester, an alkylsulfonic acid, an arylsulfonic acid, an arylalkoxy, an alkylthio, an arylthio, a cycloalkylthio, a cycloalkenyl, a cyano, an aminoalkyl, an aminoaryl, an aryl, an arylalkyl, an alkylaryl, a carboxamido, a alkylcarboxamido, an arylcarboxamido, an amidyl, a carboxyl, a carbamoyl, an alkylcarboxylic acid, an arylcarboxylic acid, an alkylcarbonyl, an arylcarbonyl, an ester, a carboxylic ester, an alkylcarboxylic ester, an arylcarboxylic ester, a haloalkoxy, a sulfonamido, an alkylsulfonamido, an arylsulfonamido, a sulfonic ester, a urea, a phosphoryl, a nitro, -T-Q, or $(\text{C}(\text{R}_e)(\text{R}_f))_k-\text{T}-\text{Q}$, or R_e and R_f taken together with the carbons to which they are attached form a carbonyl, a methanthial, a heterocyclic ring, a cycloalkyl group or a bridged cycloalkyl group; Q is -NO or -NO₂; and T is independently a covalent bond, a carbonyl, an oxygen, -S(O)_o- or -N(R_a)R_i-, wherein o is an integer from 0 to 2, R_a is a lone pair of electrons, a hydrogen or an alkyl group; R_i is a hydrogen, an alkyl, an aryl, an alkylcarboxylic acid, an aryl carboxylic acid, an alkylcarboxylic ester, an

arylcarboxylic ester, an alkylcarboxamido, an arylcarboxamido, an alkylaryl, an alkylsulfinyl, an alkylsulfonyl, an arylsulfinyl, an arylsulfonyl, a sulfonamido, a carboxamido, a carboxylic ester, an amino alkyl, an amino aryl, $-\text{CH}_2-\text{C}(\text{T}-\text{Q})(\text{R}_e)(\text{R}_f)$, or $-(\text{N}_2\text{O}_2)^-\cdot\text{M}^+$, wherein M^+ is an organic or inorganic cation; with the proviso that when R_i is $-\text{CH}_2-\text{C}(\text{T}-\text{Q})(\text{R}_e)(\text{R}_f)$ or $-(\text{N}_2\text{O}_2)^-\cdot\text{M}^+$; then "-T-Q" can be a hydrogen, an alkyl group, an alkoxyalkyl group, an aminoalkyl group, a hydroxy group or an aryl group.

104. The composition of claim 101, wherein the at least one proton pump inhibitor is a benzimidazole, a quinoline, a pyrimidine, a thiadiazole, a sulfinylnicotinamide, a thienoimidazole, or a imidazopyridine.

105. The composition of claim 104, wherein the benzimidazole is omeprazole, lansoprazole, pantoprazole, rabeprazole, leminoprazole, timoprazole, tenatoprazole, disulprazole, esomeprazole, 2-(2-benzimidazolyl)-pyridine, a tricyclic imidazole, a thienopyridine benzimidazole, a fluoroalkoxy substituted benzimidazole, a dialkoxo benzimidazole, a N-substituted 2-(pyridylalkenesulfinyl) benzimidazole, a cycloheptenepyridine, a 5-pyrrolyl-2-pyridylmethysulfinyl benzimidazole, a alkylsulfinyl benzimidazole, a fluoro-pyridylmethysulfinyl benzimidazole, an imidazo(4,5-b)pyridine, RO 18-5362 or IY 81149; wherein the quinoline is a 4-amino-3-carbonyl quinoline, a 4-amino-3-acylnaphthyride, a 4-aminoquinoline, a 4-amino-3-acylquinoline or a 3-butyryl-4-(2-methylphenylamino)-8-(2-hydroxyethoxy)quinoline; wherein the pyrimidine is a quinazoline, a tetrahydroisoquinolin-2-yl pyrimidine or YH 1885; wherein the thiadiazole is 3-substituted 1,2,4-thiadiazolo(4,5-a) benzimidazole or a 3-substituted imidazo(1,2-d)-thiadiazole; wherein the sulfinylnicotinamide is a 2-sulfinylnicotinamide; wherein the thienoimidazole is a pyridylsulfinylbenzimidazole, a pyridylsulfinyl thienoimidazole, a theinoimidazole-toluidine, a 4,5-dihydrooxazole, a

thienoimidazole-toluidine or Hoe-731; wherein the imidazopyridine is a imidazo(1,2-a)pyridine, a pyrrolo(2,3-b)pyridine or a pharmaceutically acceptable salt thereof.

106. A kit comprising at least one proton pump inhibitor or a pharmaceutically acceptable salt thereof and at least one S-nitrosothiol.

107. The kit of claim 106, wherein the S-nitrosothiol is S-nitroso-N-acetylcysteine, S-nitroso-captopril, S-nitroso-N-acetylpenicillamine, S-nitroso-homocysteine, S-nitroso-cysteine or S-nitroso-glutathione.

108. The kit of claim 106, wherein the S-nitrosothiol is:

- (i) $\text{HS}(\text{C}(\text{R}_e)(\text{R}_f))_m\text{SNO}$;
- (ii) $\text{ONS}(\text{C}(\text{R}_e)(\text{R}_f))_m\text{R}_e$; or
- (iii) $\text{H}_2\text{N}-\text{CH}(\text{CO}_2\text{H})-(\text{CH}_2)_m-\text{C}(\text{O})\text{NH}-\text{CH}(\text{CH}_2\text{SNO})-\text{C}(\text{O})\text{NH}-\text{CH}_2-\text{CO}_2\text{H}$;

wherein m is an integer from 2 to 20; R_e and R_f are each independently a hydrogen, an alkyl, a cycloalkoxy, a halogen, a hydroxy, an hydroxyalkyl, an alkoxyalkyl, an arylheterocyclic ring, an alkylaryl, a cycloalkylalkyl, a heterocyclicalkyl, an alkoxy, a haloalkoxy, an amino, an alkylamino, a dialkylamino, an arylamino, a diarylamino, an alkylarylamino, an alkoxyhaloalkyl, a haloalkoxy, a sulfonic acid, a sulfonic ester, an alkylsulfonic acid, an arylsulfonic acid, an arylalkoxy, an alkylthio, an arylthio, a cycloalkylthio, a cycloalkenyl, a cyano, an aminoalkyl, an aminoaryl, an aryl, an arylalkyl, an alkylaryl, a carboxamido, a alkylcarboxamido, an arylcarboxamido, an amidyl, a carboxyl, a carbamoyl, an alkylcarboxylic acid, an arylcarboxylic acid, an alkylcarbonyl, an arylcarbonyl, an ester, a carboxylic ester, an alkylcarboxylic ester, an arylcarboxylic ester, a haloalkoxy, a sulfonamido, an alkylsulfonamido, an arylsulfonamido, a sulfonic ester, a urea, a phosphoryl, a nitro, -T-Q, or $(\text{C}(\text{R}_e)(\text{R}_f))_k\text{-T-Q}$, or R_e and R_f taken together with the carbons to which they are attached form a carbonyl, a methanthial, a

heterocyclic ring, a cycloalkyl group or a bridged cycloalkyl group; Q is -NO or -NO₂; and T is independently a covalent bond, a carbonyl, an oxygen, -S(O)_o- or -N(R_a)R_i-, wherein o is an integer from 0 to 2, R_a is a lone pair of electrons, a hydrogen or an alkyl group; R_i is a hydrogen, an alkyl, an aryl, an alkylcarboxylic acid, an aryl carboxylic acid, an alkylcarboxylic ester, an arylcarboxylic ester, an alkylcarboxamido, an arylcarboxamido, an alkylaryl, an alkylsulfinyl, an alkylsulfonyl, an arylsulfinyl, an arylsulfonyl, a sulfonamido, a carboxamido, a carboxylic ester, an amino alkyl, an amino aryl, -CH₂-C(T-Q)(R_e)(R_f), or -(N₂O₂-)•M⁺, wherein M⁺ is an organic or inorganic cation; with the proviso that when R_i is -CH₂-C(T-Q)(R_e)(R_f) or -(N₂O₂-)•M⁺; then "-T-Q" can be a hydrogen, an alkyl group, an alkoxyalkyl group, an aminoalkyl group, a hydroxy group or an aryl group.

109. The kit of claim 106, wherein the at least one proton pump inhibitor is a benzimidazole, a quinoline, a pyrimidine, a thiadiazole, a sulfinylnicotinamide, a thienoimidazole, or a imidazopyridine.

110. The kit of claim 109, wherein the benzimidazole is omeprazole, lansoprazole, pantoprazole, rabeprazole, leminoprazole, timoprazole, tenatoprazole, disulprazole, esomeprazole, 2-(2-benzimidazolyl)-pyridine, a tricyclic imidazole, a thienopyridine benzimidazole, a fluoroalkoxy substituted benzimidazole, a dialkoxy benzimidazole, a N-substituted 2-(pyridylalkenesulfinyl) benzimidazole, a cycloheptenepyridine, a 5-pyrrolyl-2-pyridylmethysulfinyl benzimidazole, an alkylsulfinyl benzimidazole, a fluoro-pyridylmethysulfinyl benzimidazole, an imidazo(4,5-b)pyridine, RO 18-5362 or IY 81149; wherein the quinoline is a 4-amino-3-carbonyl quinoline, a 4-amino-3-acylnaphthyride, a 4-aminoquinoline, a 4-amino-3-acylquinoline or a 3-butyryl-4-(2-methylphenylamino)-8-(2-hydroxyethoxy)quinoline; wherein the pyrimidine is a quinazoline, a tetrahydroisoquinolin-2-yl

pyrimidine or YH 1885; wherein the thiadiazole is 3-substituted 1,2,4-thiadiazolo(4,5-a) benzimidazole or a 3-substituted imidazo(1,2-d)-thiadiazole; wherein the sulfinylnicotinamide is a 2-sulfinylnicotinamide; wherein the thienoimidazole is a pyridylsulfinylbenzimidazole, a pyridylsulfinyl thienoimidazole, a thienoimidazole-toluidine, a 4,5-dihydrooxazole, a thienoimidazole-toluidine or Hoe-731; wherein the imidazopyridine is a imidazo(1,2-a)pyridine, a pyrrolo(2,3-b)pyridine or a pharmaceutically acceptable salt thereof.

111. A composition comprising at least one proton pump inhibitor or a pharmaceutically acceptable salt thereof and at least one compound that induces the production of endogenous nitric oxide or endothelium-derived relaxing factor, stimulates endogenous synthesis of nitric oxide or is a substrate for nitric oxide synthase.

113. The composition of claim 111, wherein the at least one proton pump inhibitor is a benzimidazole, a quinoline, a pyrimidine, a thiadiazole, a sulfinylnicotinamide, a thienoimidazole, or a imidazopyridine.

114. The composition of claim 113, wherein the benzimidazole is omeprazole, lansoprazole, pantoprazole, rabeprazole, leminoprazole, timoprazole, tenatoprazole, disulprazole, esomeprazole, 2-(2-benzimidazolyl)-pyridine, a tricyclic imidazole, a thienopyridine benzimidazole, a fluoroalkoxy substituted benzimidazole, a dialkoxy benzimidazole, a N-substituted 2-(pyridylalkenesulfinyl) benzimidazole, a cycloheptenepyrindine, a 5-pyrrolyl-2-pyridylmethylsulfinyl benzimidazole, an alkylsulfinyl benzimidazole, a fluoro-pyridylmethylsulfinyl benzimidazole, an imidazo(4,5-b)pyridine, RO 18-5362 or IY 81149; wherein the quinoline is a 4-amino-3-carbonyl quinoline, a 4-amino-3-acylnaphthyridine, a 4-aminoquinoline, a 4-amino-3-acylquinoline or a 3-butyryl-4-(2-methylphenylamino)-8-(2-hydroxyethoxy)quinoline; wherein the pyrimidine is a quinazoline, a tetrahydroisoquinolin-2-yl

pyrimidine or YH 1885; wherein the thiadiazole is 3-substituted 1,2,4-thiadiazolo(4,5-a) benzimidazole or a 3-substituted imidazo(1,2-d)-thiadiazole; wherein the sulfinylnicotinamide is a 2-sulfinylnicotinamide; wherein the thienoimidazole is a pyridylsulfinylbenz imidazole, a pyridylsulfinyl thieno imidazole, a theinoimidazole-toluidine, a 4,5-dihydrooxazole, a thienoimidazole-toluidine or Hoe-731; wherein the imidazopyridine is a imidazo(1,2-a)pyridine, a pyrrolo(2,3-b)pyridine or a pharmaceutically acceptable salt thereof.

115. A kit comprising at least one proton pump inhibitor or a pharmaceutically acceptable salt thereof and at least one compound that induces the production of endogenous nitric oxide or endothelium-derived relaxing factor, stimulates endogenous synthesis of nitric oxide or is a substrate for nitric oxide synthase.

117. The kit of claim 115, wherein the at least one proton pump inhibitor is a benzimidazole, a quinoline, a pyrimidine, a thiadiazole, a sulfinylnicotinamide, a thienoimidazole, or a imidazopyridine.

118. The kit of claim 117, wherein the benzimidazole is omeprazole, lansoprazole, pantoprazole, rabeprazole, leminoprazole, timoprazole, tenatoprazole, disulprazole, esomeprazole, 2-(2-benzimidazolyl)-pyridine, a tricyclic imidazole, a thienopyridine benzimidazole, a fluoroalkoxy substituted benzimidazole, a dialkoxy benzimidazole, a N-substituted 2-(pyridylalkenesulfinyl) benzimidazole, a cycloheptenepyrindine, a 5-pyrrolyl-2-pyridylmethylsulfinyl benzimidazole, a alkylsulfinyl benzimidazole, a fluoro-pyridylmethylsulfinyl benzimidazole, an imidazo(4,5-b)pyridine, RO 18-5362 or IY 81149; wherein the quinoline is a 4-amino-3-carbonyl quinoline, a 4-amino-3-acylnaphthyride, a 4-aminoquinoline, a 4-amino-3-acylquinoline or a 3-butyryl-4-(2-methylphenylamino)-8-(2-hydroxyethoxy)quinoline; wherein the pyrimidine is a quinazoline, a tetrahydroisoquinolin-2-yl

pyrimidine or YH 1885; wherein the thiadiazole is 3-substituted 1,2,4-thiadiazolo(4,5-a) benzimidazole or a 3-substituted imidazo(1,2-d)-thiadiazole; wherein the sulfinylnicotinamide is a 2-sulfinylnicotinamide; wherein the thienoimidazole is a pyridylsulfinylbenz imidazole, a pyridylsulfinyl thieno imidazole, a theinoimidazole-toluidine, a 4,5-dihydrooxazole, a thienoimidazole-toluidine or Hoe-731; wherein the imidazopyridine is a imidazo(1,2-a)pyridine, a pyrrolo(2,3-b)pyridine or a pharmaceutically acceptable salt thereof.